生 物 試 験 部 門

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◇研究目的

本部門では，和漢薬の新しい薬効評価法を確立するための基礎研究，和漢薬の中枢作用を定量的に評価し，その作用本体を追求する研究及びその作用機序を分子レベルで明らかにすることを目的とした研究を行っている。

◇研究概要

Ⅰ．和漢薬の新しい薬効評価法を確立するための基礎的研究

1）脳血管性痴呆病態モデル動物の確立とそれによる和漢薬および抗痴呆薬の薬効評価
2）情動ストレス反応の不安・うつ病態モデルとしての応用と和漢薬作用
3）新規リード化合物の開発をめざした各種民族薬の薬理作用の探索と作用機構の解析

Ⅱ．中枢作用薬の神経薬理学的研究

1）心理的ストレス反応に関わる神経機構，受容体機能修飾因子，分子機序の解析
2）神経伝達物質の脳内動態および代謝回転の解析と薬物作用

Ⅲ．遺伝子発現を指標とした薬物作用の解明と和漢薬作用に関する研究

1）慢性脳虚血により発現する脳内遺伝子のクローニングとその機能解析
2）うつ病態関連脳内遺伝子の発現変化と抗うつ薬・和漢薬の作用解析

◇原　著

1）**Tohda M., Abdel-Fattah Mohamed A.-F., Nakamura S. and Watanabe H.:Effects of Hochu-ekki-to (Bu-Zhong-Yi-Qi-Tang), a Kampo medicine, on serotonin 2C subtype receptor-evoked current response and the receptor mRNA expression. Journal of Traditional Medicines 17: 34-40, 2000.**

Abstract : Hochi-ekki-to (HET, Bu-Zhong-Yi-Qi-Tang, Formula repletionis animelis et supletionis medii) is one of the Kampo medicine which has been used for improving disturbance and imbalance in the homeostatic condition of the body. Repeated treatment with HET (5.7 g/kg as estimated galenicals, p.o.) enhanced the serotonin 2C subtype receptor (5-HT2CR) mRNA expression in rat brain as effectively as 20 mg/kg imipramine p.o. HET at only 5 μg/ml as estimated galenicals evoked two types of inward current: one was of the metabotropic type and the other was of the ionotropic type. The metabotropic type current, which was expected to have strong intensity compared with that evoked by seretonin, was blocked by prior treatment with 10 μM mianserin, an antagonist of 5-HT2CR. These results suggest that HET contains strong 5-HT2CR agonistic factor(s).

2）**Pinna G., Uzunova V., Matsumoto K., Puia G., Mienville J.-M., Costa E. and Guidotti A.: Brain allopregnanolone regulates the potency of the $GABA_A$ receptor agonist muscimol. Neuropharmacology 39:440-448, 2000.**

Abstract : Allopregnanolone (ALLO), a potent positive-allosteric modulator of the action of GABA at $GABA_A$ receptors, is synthesized in the brain from progesterone by the sequential action of two enzymes: 5α-reductase and 3α-hydroxysteroidoxidoreductase. The concentration of ALLO in various parts of the mouse brain varies substantially, from 15 pmol/g in the olfactory bulb, to approximately 6 pmol/g in the frontoparietal cortex, and 2.7 pmol/g in the cerebellum. The systemic administration of 48 μmol/kg of the Type I and Type II 5α-reductase inhibitor, (17β)-17[bis(1-methylethyl)amino carbonyl] androsta-3, 5-diene-3-carboxylic acid (SKF 105,111), reduced brain ALLO content by 80-90% in 30 min; the rate constant (κ) of ALLO decrease in each brain area can be utilized to establish the rate of ALLO biosynthesis, which is higher in the olfactory bulb (62 pmol/g/h) than in the frontoparietal cortex (24 pmol/g/h) or cerebellum (11 pmol/g/h). The duration of the righting reflex loss elicited by the potent $GABA_A$ receptor agonist muscimol was reduced in SKF 105,111-treated ALLO-depleted mice. SKF 105,111 treatment had no effect on muscimol metabolism or on brain levels of pregnenolone and progesterone; however, the brain levels of 5α-DHP, the precursor of ALLO, were also decreased. Administration of ALLO at a dose of 15 μmol/kg ip by itself did not alter the muscimol-induced loss of the righting reflex; but it completely blocked the effect of SKF 105,111. To elucidate the possible molecular mechanism by which a decrease of brain ALLO content can shorten the duration of the righting reflex loss elicited by muscimol, we patch-clamped neocortical pyramidal neurons of mice pretreated with SKF 105,111 or vehicle, and studied the efficiency of muscimol in eliciting Cl^- currents. The current amplitude was significantly smaller in neurons from SKF 105,111-treated mice, especially at lower doses (0.1-1 μM) of muscimol, and the muscimol dose-response (0.1-10 μM) relationship displayed cooperativity (nH=1.4). These data suggest that ALLO synthesized in brain plays an important physiological permissive role in the modulation of GABA-gated Cl^- channel function.

3）**Yamada S., Uchida S., Naito T., Urayama A., Kimura R., Murakami Y., Matsumoto K and Watanabe H.: Increase in receptor binding affinity for nimodipine in the rat brain with permanent occlusion of bilateral carotid arteries. Life Sciences 66:1351-1357, 2000.**

Abstract : The permanent occlusion of bilateral common carotid arteries (2VO) in rats has been shown to cause progressive and long-lasting cognitive deficits which may be due to impairment of memory retention and/or memory recall process. To clarify the function of voltage dependent calcium channels and the receptor binding of nimodipine by chronic cerebral ischemia, we examined specific (+)-[^{3}H]PN 200-110 binding and the effect of oral administration

of nimodipine in brain regions and hearts of rats, at 2 weeks to 4 months after permanent 2VO. There was no significant difference in either dissociation constant (Kd) or maximal number of binding sites (Bmax) for (+)-[^{3}H]PN 200-110 in the cerebral cortex, hippocampus, corpus striatum and thalamus between 2VO and sham rats. In addition, *in vitro* inhibitory effect of nimodipine on cerebral cortical (+)-[^{3}H]PN 200-110 binding in 2VO rats was similar to that in sham rats. Compared to control rats, oral administration of nimodipine to both 2VO and sham rats at 2 months after permanent 2VO brought about a significant increase in Kd values of specific (+)-[^{3}H]PN 200-110 binding in the cerebral cortex, hippocampus, thalamus and myocardium, and the increase in Kd values was much larger in brain regions of 2VO rats than sham rats. However, the increase in Kd values in the myocardium did not differ between 2VO and sham rats. This observation suggests an increased *in vivo* binding affinity for nimodipine in chronic ischemic brain. In conclusion, the present study has shown that oral administration of nimodipine may cause a greater occupation *in vivo* of 1,4-dihydropyridine (DHP) calcium channel antagonist receptors in brains of permanent 2VO rats than in sham rats. Thus, nimodipine may be pharmacologically effective in preventing brain dysfunction due to cerebral ischemia i*n vivo.*

4）**Murakami Y., Ikenoya M., Matsumoto K., Li H.B. and Watanabe H.:Ameliorative effect of tacrine on spatial memory deficit in chronic two vessel occluded rats is reversible and mediated by muscarinic M1 receptor stimulation. Behavioural Brain Research 109:83-90, 2000.**

Abstract : Our previous study demonstrated that permanent two vessel occlusion (2VO)-induced working memory deficit was improved by daily administration of tacrine, a cholinesterase inhibitor. In this study, we investigated the mechanism underlying the effects of tacrine in 2VO rats using the eight-arm radial maze task. Daily administration of tacrine (0.1 or 0.3 mg/kg i.p.) started 5 weeks after the 2VO operation significantly improved the maze performance. In the delay-interposition task, a significant impairment of the maze performance was observed in the tacrine (0.3 mg/kg, i.p.)-treated rats at a delay of 90 min but not delays of 5 or 30 min. Sham operated rats were not affected by delay. After leaving animals with no further treatment for 4 weeks, the tacrine-pretreated 2VO rats showed significantly impaired performance compared to the sham-operated control animals. However, the performance of the tacrine-pretreated 2VO rats was significantly improved by restarting the daily administration of tacrine (0.3 mg/kg, i.p.). The effect of tacrine was reversed by the muscarinic antagonist scopolamine and the selective M1 antagonist pirenzepine. Moreover, a microdialysis study revealed that tacrine (1 or 3 mg/kg, i.p.) increased the extracellular acetylcholine (ACh) level for a period of over 3 hours in the cerebral cortex of 2VO rats. These findings suggest that the ameliorative effect of tacrine on the spatial memory deficit in 2VO rats is reversible and may be mediated by stimulating the muscarinic M1 receptor via elevation of the extracellular ACh level in the brain.

5）**Tabata K., Matsumoto K. and Watanabe H.: Paeoniflorin, a major constituent of peony root, reverses muscarinic M_1-receptor antagonist-induced suppression of long-term potentiation in the rat hippocampal slice. Japanese Journal of Pharmacology 83:25-30, 2000.**

Abstract : We previously reported that paeoniflorin but not albiflorin, components of peony root, produced ameliorative effects on scopolamine-induced spatial cognitive impairment in rats. In this study, we examined the effects of paeoniflorin and muscarinic receptor antagonists on long-term potentiation (LTP) of population spike recorded from the CA1 region of the rat hippocampal slices. Bath applications of an M_1- and M_2-receptor antagonist scopolamine, and a selective M_1-receptor antagonist pirenzepine, at a concentration of 10 μM, significantly suppressed LTP, whereas AF-DX116, a selective M_2-receptor antagonist, failed to affect it. Paeoniflorin (0.1-1 μM), which alone was ineffective on LTP induction, significantly reversed the suppressive effects of scopolamine and pirenzepine (10 μM). In contrast, albiflorin (0.1-1 μM) had no effect on the scopolamine-induced LTP suppression. These results suggest that paeoniflorin reversal of the muscarinic M_1-receptor-mediated inhibition of LTP may be implicated in the ameliorative effect of paeoniflorin on spatial cognitive impairment caused by cholinergic dysfunction.

6) **Yobimoto K., Matsumoto K., Nguyen T.T.H., Kasai R., Yamasaki K. and Watanabe H.: Suppressive effects of Vietnamese ginseng saponin and its major component majonoside-R2 on psychological stress-induced enhancement of lipid peroxidation in the mouse brain. Pharmacology Biochemistry & Behavior 66:661-665, 2000.**

Abstract : We investigated the in vivo effects of Vietnamese ginseng saponin (VG saponin) and its major component majonoside-R2 (MR2) on psychological stress-iniduced enhancement of lipid peroxidation in the mouse brain. Psychological stress exposure using a communication box system for 4 h significantly increased the content of thiobarbituric acid reactive substance (TBARS), an index of lipid peroxidation activity, in the brain. Pretreatment with VG saponin (15-25 mg/kg, PO) and MR2 (1-10 mg/kg, IP) significantly attenuated the psychological stress-induced increase in TBARS content in the brain. The aglycone of MR2 (MR2-aglycone: 1.2 mg/kg, IP), at the equivalent dose of MR2 (i.e., 3 mg/kg, IP), also produced the suppressive effect on the increase in the TBARS content. The in vivo suppressive effect of MR2 was dose dependently attenuated by flumazenil (3 and 10 mg/kg, IP), a benzodiazepine receptor antagonist, and pregnenolone sulfate (10 mg/kg, IP), a neurosteroidal negative allosteric modulator of $GABA_A$ receptors. These findings suggest that VG saponin and its major component MR2 have preventive effects on the psychological stress-induced brain cell membrane damage, and that the effect of MR2 is partly due to enhancement of $GABA_A$-ergic systems in the brain.

7) **Abdel-Fattah Mohamed A.-F., Matsumoto K. and Watanabe H.: Antinociceptive effects of *Nigella sativa* oil and its major component, thymoquinone, in mice. European Journal of Pharmacology 400:89-97, 2000.**

Abstract : The antinociceptive effects of *Nigella sativa* oil and its major component, thymoquinone, were examined in mice. The p.o. administratioin of *N. sativa* oil (50-400 mg/kg) dose-dependently suppressed the nociceptive response in the hot-plate test, tail-pinch test, acetic acid-induced writhing test an din the early phase of the formalin test. The systemic administration (2.5-10 mg/kg, p.o. and 1-6 mg/kg, i.p.) and the i.c.v. injection (1-4 μ g/mouse) of thymoquinone attenuated the nociceptive response in not only the early phase but also the late phase of the formalin test. Naloxone injected s.c. (1 mg/kg) significantly blocked *N. sativa* oil-and thymoquinone-induced antinociception in the early phase of the formalin test. Moreover, the i.c.v. injection of naloxone (10 μg/mouse), the μ1-opioid receptor antagonist, naloxonazine (1-5 μg/mouse), or the κ-opioid receptor antagonist, nor-binaltorphimine (1-5 μg/mouse), significantly reversed thymoquinone-induced antinociception in the early phase but not the late phase of the formalin test, wherease the δ-opioid receptor antagonist, naltrindole (1-5 ng/mouse, i.c.v.), had no effect on either phase. The antinociceptive effect of morphine was significantly reduced in thymoquinone- and *N. sativa* oil-tolerant mice, but not vice versa. These results suggest that *N. sativa* oil and thymoquinone produce antinociceptive effects though indirect activation of the supraspinal μ1- and κ-opioid receptor subtypes.

8) **Vajragupta O., Monthakantirat O., Wongkrajang Y., Watanabe H. and Peungvicha P.: Chroman amide 12P inhibition of lipid peroxidation and protection against learning and memory impairment. Life Sciences 67:1725-1734, 2000.**

Abstract : Structure modification of the cerebroprotective chroman amide 12 to improve the drug delivery to the target organ by protecting the active hydroxy functional group was carried out in this study. Chroman amide 12P, which the O-acetyl group was served to protect the active group to be delivered to the target organ, was synthesized. *Ex vivo* antilipid peroxidation activity of 12P was significantly greater than the activity of 12 while the *in vitro* inhibition of 12P was found to be lower. These indicated that 12P with protected active group effectively reached the brain, the target site, but *in vitro*, 12P was unable to release its parent or released slowly. Neuropharmacological effect of 12P was investigated in mice. 12 and 12P (50-100 mg/kg, i.p.) showed significant suppression on the hypermotility induced by methamphetamine. 12P (100 mg/kg, i.p.) was more potent than 12, 54.36% and 38.73%

suppression, respectively. The result suggested the enhancement of brain delivery and the antagonism against aberrant dopamine release. In the water maze test, 12P (200 mg/kg) as well as tacrine (3 mg/kg) significantly reduced the learning and memory impairment induced by scopolamine (0.5 mg/kg). The results support the enhanced brain delivery and the additional role of radical scavengers in the modulation of brain neurotransmitters in the aberrant condition.

9) **Vajragupta O., Toasaksiri S., Boonyarat C., Wongkrajang Y., Peungvicha P., Watanabe H. and Boonchoong P.: Chroman amide and nicotinyl amide derivatives: inhibition of lipid peroxidation and protection. Free Radical Research 32:145-155, 2000.**

Abstract : A series of chroman amide and nicotinyl amide derivatives was designed and synthesized for the treatment of traumatic and ischemic CNS injury, Five compounds were significantly more potent inhibitors of lipid peroxidation *in vitro* than the reference antioxidant, trolox ($p<0.01$). Quantitative structure activity studies demonstrated that the inhibitory action was related to the ability to donate electrons, charge on hydroxy group and E_{LUMO}, to scavenging radicals and to the lipophilicity log *P*, which determines penetration of membrane lipids. ESR study indicated the ability of 12 to scavenge the hydroxyl radicals. The most promising compound, [(3,4-dihydro-6-hydroxy-2,5,7,8-tetramethyl-2H-1-benzopyran-2yl)carbonyl]-3'-(aminoethyl) indole (12), inhibited *ex vivo* lipid peroxidation in a head injury model and showed potent *in vivo* neuroprotective efficacy Improvement of neurological recovery within 1 h of injury (grip test score) by as much as 200% was observed together with significant anti-anoxia activity. Compound 12 was a potent antagonist of methamphetamine-induced hypermotility resulting from dopamine release in the mouse brain. These results support the importance of cerebroprotective radical-scavenging agents for the treatment of traumatic injury and anoxia as well as provide additional evidence for the role of oxygen radicals and dopamine in brain damage.

10) **Skalko-Basnet N., Tohda M. and Watanabe H.: Delivery of antisense oligonucleotides to neuroblastoma cells. Neuroreport 11:3117-3121, 2000.**

Abstract : pH-Sensitive liposomes composed of dioleoylphosphatidylethanolamine and cholesterol hemisuccinate (3:2 mol/mol) were applied in delivery of antisense oligodeoxynucleotides (asODN) into NG 108-15 neuroblastoma and glioma cells. Fluorescently labelled asODN were entrapped in liposomes by a modified freeze-thawing method (20% encapsulation efficiency). The uptake of asODN (free or entrapped in liposomes) by NG 108-15 cells was monitored by fluorescence-activated cell sorting and confocal microscopy. Delivery of asODN was significantly improved when antisense were entrapped in liposomes as compared to free (nonliposomal) asODN. The uptake was dose-dependent and optimum was achieved after 2 h incubation.

11) **Xu J.H., Murakami Y., Matsumoto K., Tohda M., Watanabe H., Zhang S.H., Yu Q.H. and Shen J.: Protective effect of Oren-gedoku-to (Huang-Lian-Jie-Du-Tang) against impairment of learning and memory induced by transient cerebral ischemia in mice. Journal of Ethnopharmacology 73:405-413, 2000.**

Abstract : The protective effect of Oren-gedoku-to (OGT; Huang-Lian-Jie-Du-Tang), a traditional Chinese medicine, against impairment of learning and memory impairment induced by transient cerebral ischemia was investigated in mice. The cerebral ischemia caused a reduction of step-down latency and an increase of step-down errors in the passive avoidance task. Pretreatment with oral administration of OGT (2, 4 or 8 g of herbs/kg) once daily for 5 days significantly prolonged the step-down latency and decreased the step-down errors as compared with those of sham-operated controls. In the Morris water maze test, the cerebral ischemia caused an increase in the latency until finding the platform in the training trial and a decrease in the percentage of swimming in the quadrant of the former platform in the probe trial. OGT (2, 4 and 8 g/kg, p.o.) markedly shortened the latency of escaping onto the platform

in the training trial and increased the percentage of crossing the former platform quadrant in the probe trial. A reference drug, tacrine (0.5 and 1.0 mg/kg, p.o.), prevented the reduction of step-down latency in the passive avoidance task and shortened the escape latency in the Morris water maze task. Furthermore, OGT significantly protected against cerebral ischemia-induced reduction in the acetylcholine (ACh) content of the cerebral cortex, hippocampus and striatum. These results indicate that the protective effects of OGT against the impairment of learning and memory induced by transient cerebral ischemia may be associated with preventing the decrease in the ACh content of the mouse brain.

12) **Abdel-Fattah Mohamed A.-F., Matsumoto K., Tabata K., Takayama H., Kitajima M., Aimi N. and Watanabe H.: Effects of *Uncaria tomentosa* total alkaloid and its components on experimental amnesia in mice: Elucidation using the passive avoidance test. Journal of Pharmacy and Pharmacology 52:1553 -1561, 2000.**

Abstract : The effects of *Uncaria tomentosa* total alkaloid and its oxindole alkaloid components, uncarine E, uncarine C, mitraphylline, rhynchophylline and isorhynchophylline, on the impairment of retention performance caused by amnesic drugs were investigated using a step-down type passive avoidance test in mice. In this test, the retention performance of animals treated with the amnesic and test drugs before training was assessed 24 hrs after training. *Uncaria tomentosa* total alkaloid (10-20 mg/kg, i.p.) and the alkaloid components (10-40 mg/kg, i.p.), as well as the muscarinic receptor agonist oxotremorine (0.01 mg/kg, i.p.), significantly attenuated the deficit in retention performance induced by the muscarinic receptor antagonist scopolamine (3 mg/kg, i.p.). The effective doses of uncarine C and mitraphylline were larger than those of other alkaloid components. Uncarine E (20 mg/kg, i.p.) also blocked the impairment of passive avoidance performance caused by the nicotinic receptor antagonist mecamylamine (15 mg/kg i.p.) and the N-methyl-D-aspartate (NMDA) receptor antagonist (±)-3-(2-carboxypiperazin-4-yl)-propyl-1-phosphonic acid (CPP; 7.5 mg/kg, i.p.), but it failed to affect the deficit caused by the benzodiazepine receptor agonist diazepam (2 mg/kg, i.p.). Rhynchophylline significantly reduced the mecamylamine-induced deficit in passive avoidance behavior, but it failed to attenuate the effects of CPP and diazepam. These results suggest that *Uncaria tomentosa* total alkaloids exert a beneficial effect on memory impairment induced by the dysfunction of cholinergic systems in the brain and that the effect of the total alkaloids is partly attributed to the oxindole alkaloids tested. Moreover, the present findings raised the possibility that the glutamatergic systems are implicated in the anti-amnesic effect of uncarine E.

◇総　説

1）松本欣三，渡辺裕司：ストレスによる薬物誘発睡眠障害と和漢薬—特に当帰とそのフタライド成分の影響について—. 漢方と最新治療，9：27–34，2000.

◇学会報告

1）アブデル・ファッターモハメド，松本欣三，渡辺裕司：マウス・ホルマリン試験における thymoquinone の抗侵害受容作用：μ1およびκ-オピオイド受容体の関与. 第73回日本薬理学会年会，2000，3/23–25，横浜.

2）松本欣三，董而博，東田道久，渡辺裕司：コルチコステロンによるマウス視床下部 diazepam binding inhibitor (DBI) 遺伝子発現及びペントバルビタール誘発睡眠の変化. 第73回日本薬理学会年会，2000，3/23–25，横浜.

3）中島隆太郎，東田道久，渡辺裕司: 慢性脳虚血初期のラット脳中において発現量が増大する遺伝子の.第73回日本薬理学会年会，2000，3/23–25，横浜.

4）田畑恵市，松本欣三，渡辺裕司: ムスカリン性 M_1 受容体を介したラット海馬長期増強現象の抑制作用に対する芍薬成分ペオニフロリンの効果：in vitro 標本における検討. 第73回日本薬理学会年会，2000，

3/23–25, 横浜.

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6）Watanabe H.: Stress and traditional medicine. An International Conference on Life Science and Clinical medicine, 2000, 4/19-21, Beijing.

7）Watanabe H.: Anti-dementia effects of Gouten-san and Si-Wu-Tang. The 2nd Congress of Asia Society of Toxicology, 2000, 8/23-25, Cheju.

8）張紹輝，東田道久，村上孝寿，松本欣三，渡辺裕司，小島暁：スコポラミン誘発のマウス学習行動障害に対する四物湯及び構成生薬の影響．第17回和漢医薬学会大会，2000，9/2–3，東浦.

9）野村浩明，松本欣三，高畑廣紀，A. Guidotti, E. Costa，渡辺裕司：マウスの不安行動発現における allopregnanolone の役割．第51回日本薬理学会北部会，2000，9/30，富山.

10）Watanabe H.: Anti-dementia effects of traditional medicine. Third international congress on phytomedicine, 2000, 10/11-13, Munich.

11）東田道久，野村靖幸，東田陽博，渡辺裕司：NG108-15細胞に存在するイノシトールリン脂質代謝に共役しない 5-HT2C 受容体様 mRNA の構造．第44回日本神経化学会（金沢）大会，2000，10/18–20，金沢.

12）Watanabe H.: Research collaboration between Japan and Thailand under JSPS-NRCT core university exchange program in the next five years. NRCT-JSPS core university system on pharmaceutical sciences — The fifth joint seminar natural medicines, 2000, 11/15-17, Bangkok.

13）Watanabe H.: Anti-dementia effects of traditional medicine. The 8th world congress on clinical nutrition, 2000, 12/17-20, Phitsanulok (Thailand).

◇その他

1）松本欣三：国際伝統医薬フォーラムに参加して．日本醫事新報別冊，3953：44–45，2000.

◇共同研究

1）相見則郎，高山廣光：千葉大学薬学部，「タイ薬用植物中のインドールアルカロイド類に関する創薬基礎科学研究」1994，4–

2）山崎和男，笠井良次：広島大学医学部，グエン・チー・スー・フォン：ベトナム薬用人参センター，「ベトナム人参の薬理作用の研究」1994，4–

3）Erminio Costa, Alessandro Guidotti：イリノイ州立大学シカゴ校精神医学研究所，「ストレス病態における神経活性ステロイドの役割」1997，4–

◇研究費取得状況

1）文部省科学研究費，基盤研究B（2）（代表：渡辺裕司）「白質脳症モデル動物に関する薬理学的研究」380万

2）文部省科学研究費，基盤研究B（2）（代表：東田道久）「慢性虚血ラット脳中で発現変化する新規単離因子の生理機能・発現制御機構の解明」660万

3）平成12年度文部省創造開発研究費（代表：松本欣三）「脳内神経ステロイド系障害に対する天然薬物作用の研究」131万

4）平成12年度横田基金教育研究助成（代表：村上孝寿）「Thymoquinone の中枢 opioid 系興奮作用の解析と記憶障害改善効果の検討」10万

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◇学位取得者

論文博士：
村上孝寿：慢性脳循環障害ラットの学習行動障害に対するコリン作動薬およびカルシウム拮抗薬の影響とその作用機序